Childhood Cardiometabolic Outcomes of Maternal Obesity During Pregnancy

The Generation R Study

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Abstract—Maternal prepregnancy obesity is associated with impaired cardiometabolic health in offspring. Whether these associations reflect direct intrauterine causal mechanisms remains unclear. In a population-based prospective cohort study among 4871 mothers, fathers, and their children, we examined the associations of both maternal and paternal prepregnancy body mass index (BMI) with childhood body fat distribution and cardiometabolic outcomes and explored whether any association was explained by pregnancy, birth, and childhood factors. We measured childhood BMI, total body and abdominal fat distribution, blood pressure, and blood levels of lipids, insulin, and C-peptide at the age of 6 years. We observed that higher maternal and paternal prepregnancy BMI were associated with higher childhood BMI, total body and abdominal fat mass measures, systolic blood pressure, and insulin levels and lower high-density lipoprotein cholesterol levels ($P<0.05$). Stronger associations were present for maternal than paternal BMI, with statistical support for heterogeneity between these associations. The associations for childhood fat mass and cardiometabolic outcomes attenuated after adjustment for childhood current BMI. Compared with children from normal-weight mothers, those from obese mothers had increased risks of childhood overweight (odds ratio, 3.84 [95% confidence interval, 3.01–4.90]) and clustering of cardiometabolic risk factors (odds ratio, 3.00 [95% confidence interval, 2.09–4.34]). Smaller effect estimates for these outcomes were observed for paternal obesity. In conclusion, higher maternal and paternal prepregnancy BMI were associated with an adverse cardiometabolic profile in offspring, with stronger associations present for maternal prepregnancy BMI. These findings suggest that maternal prepregnancy BMI may influence the cardiometabolic health of offspring through direct intrauterine mechanisms. **(*Hypertension*. 2014;63:683-691.)** ● **Online Data Supplement**

Key Words: blood pressure ■ body mass index ■ cohort studies ■ lipids ■ pediatric obesity ■ pregnancy

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Maternal obesity during pregnancy is associated with an adverse cardiometabolic risk profile in childhood and adulthood.[1–4] The mechanisms underlying these associations might involve increased placental transfer of nutrients during fetal development, which may cause permanent adaptations in appetite, energy metabolism, and neuroendocrine function in offspring, which predispose individuals to a greater risk of cardiometabolic disease in later life.[5] However, these associations might also reflect shared family-based, lifestyle-related characteristics or genetic factors.[5] Comparing the strength of associations of prepregnancy body mass index (BMI) from both mother and father with childhood outcomes could help in disentangling underlying mechanisms.[6,7] Stronger associations for maternal BMI suggest direct intrauterine mechanisms, whereas similar or stronger associations for paternal BMI suggest a role for shared family-based, lifestyle-related characteristics or genetic factors. To date, studies comparing associations of maternal and paternal BMI with childhood BMI have shown conflicting results.[5,8–11] Also, most previous studies did not explore associations of parental BMI with detailed childhood body and abdominal fat distribution and cardiometabolic outcomes. It further remains unclear whether differences in magnitude of associations of parental BMI with childhood outcomes are present across the full range of BMI or confined to parental obesity only.

Therefore, in a population-based prospective cohort study among 4871 children and their parents, we examined the associations of maternal and paternal prepregnancy BMI with childhood BMI, total body and abdominal fat distribution, and cardiometabolic risk factors. We also explored whether these associations are present across the full range of BMI and explained by pregnancy, birth, or childhood characteristics.

Received October 24, 2013; first decision November 17, 2013; revision accepted December 5, 2013.

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The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.113.02671/-/DC1.

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Methods

Study Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early pregnancy onward in Rotterdam, The Netherlands.[12] The local medical ethical committee approved the study. Written informed consent was obtained from all mothers. In total, 6959 mothers had information about prepregnancy BMI available and gave birth to singleton live-born children. Missing information about prepregnancy BMI was mainly because of later enrollment in the study and nonparticipation in the first questionnaire. We excluded mothers and their children without follow-up data available. The population for analysis included 4871 (70%) children and their parents (flow chart given in Figure S1 in the online-only Data Supplement).

Parental Anthropometrics

At enrollment, we measured maternal and paternal height (cm) and weight (kg) without shoes and heavy clothing. BMI (kg/m^2) was calculated. Information about maternal weight just before pregnancy was obtained by questionnaire. In our population for analysis, 52.3% of all mothers were enrolled before a gestational age of 14 weeks. Correlation of prepregnancy weight, obtained by questionnaire, and weight measured at enrollment was 0.94 (P<0.001). Prepregnancy maternal and paternal BMI were categorized into 4 categories (underweight [<20 kg/m^2], normal weight [20–24.9 kg/m^2], overweight [25–29.9 kg/m^2], and obese [≥30 kg/m^2]).

Childhood Body Fat and Cardiometabolic Outcomes

All children were invited to participate in detailed body fat and cardiometabolic follow-up measurements at the age of 6 years. We measured height and weight without shoes and heavy clothing and calculated BMI. Childhood underweight, normal weight, overweight, and obesity were defined by the International Obesity Task Force cutoffs.[13] Body fat was measured by dual-energy x-ray absorptiometry (iDXA; General Electrics–Lunar, 2008, Madison, WI).[14] Total fat mass was calculated as percentage of total body weight measured by dual-energy x-ray absorptiometry. We calculated android/gynoid fat mass ratio.[14] We performed abdominal ultrasound examinations as described previously.[15,16] Subcutaneous and preperitoneal fat mass areas were measured as areas of 2 cm length along the midline starting from the reference point in the direction of the navel.

Systolic and diastolic blood pressures were measured at the right brachial artery, 4× with 1-minute intervals, using the validated automatic sphygmanometer Datascope Accutor Plus TM (Paramus, NJ).[17] We used the mean systolic and diastolic blood pressure values using the last 3 blood pressure measurements.

We obtained 30-minute fasting venous blood samples and measured total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, insulin, and C-peptide levels.

In line with previous definitions used among pediatric populations to define childhood metabolic syndrome–like phenotype,[18] we defined clustering of cardiometabolic risk factors as having any of the 3 or more following components: android fat mass % ≥75th percentile; systolic or diastolic blood pressure ≥75th percentile; high-density lipoprotein cholesterol ≤25th percentile or triglycerides ≥75th percentile; and insulin level ≥75th percentile. We used android fat mass as percentage of total body fat mass, which was used as proxy for waist circumference because waist circumference was not available.

Covariates

Information on maternal and paternal age, education level, ethnicity, and maternal folic acid supplement use was obtained at enrollment.[12] Information on maternal smoking and alcohol consumption was assessed by questionnaires during pregnancy. First trimester maternal nutritional information was obtained by food frequency questionnaire.[19] Maternal weight gain until a gestational age of 30 weeks (median, 30.2 weeks; 95% range, 28.5–32.9) was measured. Information about pregnancy complications, mode of delivery and childhood sex, gestational age, and weight and length at birth was obtained from medical records.[20,21] Early childhood growth was measured at community health centers at 24 months. Information about breast-feeding, timing of introduction of solid foods, and average television-watching time was obtained by questionnaires.[12]

Statistical Analysis

First, differences in subject characteristics between maternal BMI categories were examined with 1-way ANOVA tests and χ^2 tests. Second, we examined the associations of maternal and paternal BMI singularly and simultaneously with childhood outcomes in 4 linear regression models: (1) a basic model including child's age and sex; (2) a confounder model, which additionally included covariates selected on the basis of their associations with the outcomes of interest based on previous studies or a change in effect estimate >10%. We included childhood height as covariate in all models focused on fat mass outcomes; (3) an intermediate model, which additionally included maternal pregnancy complications, weight gain during pregnancy, gestational age and weight at birth, infant growth until 2 years of age, and current childhood BMI; and (4) a fully adjusted model including all covariates. The confounder model was considered as the main model. Third, we examined the associations of maternal and paternal underweight, normal weight, overweight, and obesity with childhood cardiometabolic outcomes using linear regression models and with the risks of childhood overweight and childhood clustering of cardiometabolic risk factors using logistic regression models. For all analyses, we transformed non-normally distributed childhood outcome variables. We constructed standard deviation scores (SDS) values [(observed value−mean)/SD] for parental BMI and childhood outcomes to enable comparison of effect estimates. We examined potential interactions between maternal BMI and paternal BMI, gestational weight gain, sex, ethnicity, gestational age–adjusted birth weight, and childhood BMI for these associations, but after taking multiple testing into account, no significant interactions were present, and no further stratified analyses were performed. Missing data of covariates were imputed using multiple imputations. All analyses were performed using Statistical Package of Social Sciences version 17.0 for Windows (SPSS Inc, Chicago, IL).

Results

Subject Characteristics

Characteristics of the included mothers, fathers, and children are given in Table 1. Correlation coefficients among maternal, paternal, and childhood cardiometabolic outcomes are shown in Table S1. Table S2 shows that mothers without offspring follow-up data were more likely to be less educated and from non-European descent.

Parental BMI and Childhood Cardiometabolic Outcomes

Table 2 shows the associations of parental BMI with childhood outcomes per SDS change and the role of potential intermediates. In the confounder model, 1-SDS higher maternal and paternal BMI were associated with 0.25-SDS (95% confidence interval [CI], 0.23–0.28) and 0.22-SDS (95% CI, 0.19–0.24) higher childhood BMI, respectively (P value for statistical difference between these associations <0.05). Including both maternal and paternal BMI in the same model only slightly attenuated these effect estimates. The association of maternal BMI with childhood BMI was not explained by pregnancy complications and gestational weight gain. The associations of both maternal and paternal BMI with childhood BMI slightly attenuated after adjustment for birth characteristics and infant growth. In the fully adjusted model, both

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Table 1. Characteristics of Mothers, Fathers, and Their Children (N=4871)

Characteristics	Total Group (N=4871)	Maternal Underweight (n=738)	Maternal Normal Weight (n=2789)	Maternal Overweight (n=940)	Maternal Obesity (n=404)	*P* Value*
Maternal characteristics						
Age, median (95% range), y	30.9 (19.9–39.4)	30.4 (19.1–38.7)	31.2 (19.8–39.6)	30.8 (20.7–39.5)	30.3 (20.6–39.4)	<0.01
Gestational age at intake, median (95% range), wk	13.8 (9.9–24.2)	13.8 (9.8–24.1)	13.8 (10.0–24.1)	13.9 (9.8–24.1)	14.2 (10.1–24.9)	0.38
BMI, mean (SD), kg/m^2	23.6 (4.2)	18.9 (0.9)	22.3 (1.4)	26.9 (1.4)	33.9 (3.7)	<0.01
Weight gain during pregnancy, mean (SD), kg	10.5 (4.9)	11.1 (3.9)	11.0 (4.4)	9.8 (5.2)	7.2 (7.0)	<0.01
Education (higher education), n (%)	2198 (46.3)	355 (49.0)	1422 (51.0)	336 (37.0)	85 (22.4)	<0.01
Race/ethnicity (Dutch or European), n (%)	2985 (61.5)	481 (65.4)	1826 (65.7)	483 (51.5)	195 (48.9)	<0.01
Marital status (married), n (%)	2379 (50.0)	327 (45.2)	1330 (48.5)	511 (56.2)	211(54.8)	<0.01
Parity (nulliparous), n (%)	2833 (58.2)	472 (64.0)	1711 (61.3)	470 (50.0)	180 (44.6)	<0.01
Total energy intake, mean (SD), kcal	2052 (551)	2110 (562)	2075 (542)	1996 (541)	1907 (583)	<0.01
Folic acid supplement use (yes), n (%)	3040 (75.1)	453 (76.7)	1837 (78.2)	537 (69.2)	213 (63.9)	<0.01
Smoking during pregnancy (yes), n (%)	1187 (25.5)	199 (28.0)	660 (24.7)	226 (25.5)	102 (26.5)	0.31
Alcohol consumption during pregnancy (yes), n (%)	2509 (54.0)	417 (59.0)	1550 (57.9)	411 (46.5)	131 (34.3)	<0.01
Maternal pregnancy complications						
Gestational hypertension, n (%)	206 (4.4)	15 (2.1)	90 (3.3)	57 (6.1)	44 (10.9)	<0.01
Preeclampsia, n (%)	86 (1.9)	12 (1.7)	35 (1.3)	22 (2.6)	17 (5.2)	<0.01
Gestational diabetes mellitus, n (%)	51 (1.1)	3 (0.4)	12 (0.4)	23 (2.6)	13 (3.3)	<0.01
Paternal characteristics						
Age, median (95% range), y	33.2 (22.3–46.1)	32.8 (21.7–45.8)	33.2 (22.3–45.9)	33.1 (22.3–46.0)	32.8 (24.1–48.9)	0.26
BMI, mean (SD), kg/m^2	25.3 (3.4)	24.3 (3.0)	25.1 (3.2)	26.1 (3.6)	27.0 (4.5)	<0.01
Paternal education (higher education), n (%)	1738 (52.4)	278 (55.9)	1124 (55.9)	269 (45.9)	67 (29.9)	<0.01
Race/ethnicity (Dutch or European), n (%)	2620 (71.0)	396 (70.6)	1624 (73.6)	433 (65.7)	167 (63.7)	<0.01
Birth and infant characteristics						
Men, n (%)	2444 (50.2)	389 (52.7)	1399 (50.2)	460 (48.9)	196 (48.5)	0.40
Gestational age at birth, median (95% range), wk	39.9 (35.9–42.3)	40.0 (35.6–42.1)	40.1 (36.1–42.3)	40.3 (36.0–42.4)	40.0 (34.4–42.4)	<0.01
Birth weight, mean (SD), g	3435 (545)	3275 (513)	3445 (539)	3500 (543)	3504 (589)	<0.01
Caesarean delivery, n (%)	539 (12.1)	71 (10.6)	289 (11.4)	126 (14.9)	53 (13.8)	0.02
Ever breast-feeding (yes), n (%)	3566 (92.7)	545 (93.3)	2095 (93.4)	655 (92.5)	271 (87.4)	<0.01
Breast-feeding duration, median (95% range), mo	3.5 (0.5–12.0)	3.5 (0.5–12.0)	3.8 (0.5–12.0)	3.5 (0.5–12.0)	2.5 (0.5–12.0)	<0.01
Introduction of solid foods (before 6 mo), n (%)	2687 (89.5)	376 (87.9)	1613 (89.5)	490 (90.4)	208 (90.8)	<0.01
Television watching (>2 h/d), n (%)	747 (19.3)	105 (17.7)	356 (15.8)	192 (26.3)	94 (33.2)	<0.01
Childhood characteristics						
Age at follow-up, median (95% range), y	6.0 (5.6–8.0)	6.0 (5.6–8.0)	6.0 (5.6–7.9)	6.0 (5.6–7.9)	6.1 (5.6–8.1)	<0.01
BMI, mean (SD), kg/m^2	16.2 (1.9)	15.6 (1.5)	16.1 (1.6)	16.6 (2.0)	17.7 (2.8)	<0.01
Overweight or obesity, n (%)	866 (17.8)	57 (7.8)	393 (14.1)	245 (26.1)	171 (42.3)	<0.01
Total fat mass, mean (SD), %	25.0 (5.7)	23.3 (4.9)	24.4 (5.3)	26.0 (5.8)	28.8 (7.0)	<0.01

(Continued)

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Table 1. Continued

Characteristics	Total Group (N=4871)	Maternal Underweight (n=738)	Maternal Normal Weight (n=2789)	Maternal Overweight (n=940)	Maternal Obesity (n=404)	*P* Value*
Android/gynoid fat mass ratio, mean (SD)	0.25 (0.06)	0.24 (0.06)	0.25 (0.06)	0.26 (0.07)	0.29 (0.08)	<0.01
Systolic blood pressure, mean (SD), mm Hg	102.8 (8.2)	102.0 (7.9)	102.4 (8.1)	103.6 (8.4)	104.9 (8.4)	<0.01
Diastolic blood pressure, mean (SD), mm Hg	60.8 (6.9)	60.7 (6.7)	60.6 (6.8)	60.8 (6.8)	61.8 (7.2)	0.02
Total cholesterol, mean (SD), mmol/L	4.2 (0.6)	4.2 (0.6)	4.2 (0.6)	4.2 (0.6)	4.2 (0.7)	0.42
HDL cholesterol, mean (SD), mmol/L	1.3 (0.3)	1.3 (0.3)	1.4 (0.3)	1.3 (0.3)	1.3 (0.3)	0.80
LDL cholesterol, mean (SD), mmol/L	2.4 (0.6)	2.3 (0.6)	2.3 (0.6)	2.4 (0.6)	2.4 (0.5)	0.23
Triglycerides, median (95% range), mmol/L	1.0 (0.4–2.4)	0.9 (0.4–2.4)	1.0 (0.4–2.3)	0.9 (0.4–2.5)	1.0 (0.4–2.6)	0.11
Insulin, median (95% range), pmol/L	117.0 (16.1–405.8)	121.9 (13–357.7)	117.4 (15.8–394.3)	109.7 (17.7–424.4)	123.5 (14.5,493.8)	0.04
C-peptide, median (95% range), nmol/L	1.0 (0.3–2.2)	1.0 (0.3–2.0)	1.0 (0.3–2.1)	1.0 (0.3–2.3)	1.1 (0.3–2.6)	0.04
Cardiometabolic risk factor clustering, n (%)	314 (10.4)	39 (8.5)	144 (8.3)	77 (12.9)	54 (22.4)	<0.01

Values represent mean (SD), median (95% range), or number of subjects (valid %). BMI indicates body mass index; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*Differences in subject characteristics between groups were evaluated using 1-way ANOVA tests for continuous variables and χ^2 tests for proportions.

maternal and paternal BMI remained significantly associated with childhood BMI, with a significantly stronger association for maternal BMI.

Similar patterns were present for the associations of parental BMI with childhood total body and abdominal fat mass measures. Compared with paternal BMI, maternal BMI was more strongly associated with all childhood total body and abdominal fat mass measures. However, differences in the magnitude of effect estimates of maternal–offspring and paternal–offspring associations for android/gynoid fat mass ratio and abdominal preperitoneal fat mass were not statistically significant. After adjustment of these associations for current childhood BMI, only the association of maternal BMI with childhood total body fat mass remained significant.

Table 3 shows that higher maternal and paternal BMI were associated with a higher childhood systolic blood pressure (differences, 0.08 SDS [95% CI, 0.05–0.11] and 0.06 SDS [95% CI, 0.03–0.09] per SDS change in maternal and paternal BMI, respectively) but not diastolic blood pressure. These associations were largely explained by childhood BMI. In the fully adjusted model, maternal BMI, but not paternal BMI, was still associated with a higher childhood systolic blood pressure ($P<0.05$). In the confounder model, a higher maternal BMI was associated with lower childhood high-density lipoprotein cholesterol and higher insulin levels ($P<0.05$) but not with childhood total cholesterol, low-density lipoprotein cholesterol, triglycerides, and C-peptide levels (results for C-peptide not shown). Higher paternal BMI was only associated with lower childhood high-density lipoprotein cholesterol ($P<0.05$), with similar effect estimates as for maternal BMI. These associations were fully explained by childhood BMI.

Parental Obesity and Childhood Cardiometabolic Outcomes

Figure S2 shows that compared with maternal normal weight, maternal obesity was associated with a higher childhood BMI, total body and abdominal fat mass measures, systolic blood pressure, triglycerides, insulin, and C-peptide levels (all $P<0.05$). Similar, but weaker, associations were present for paternal obesity. The Figure shows that compared with maternal normal weight, maternal obesity was associated with increased risks of childhood overweight (odds ratio, 3.84 [95% CI, 3.01–4.90]) and clustering of cardiometabolic risk factors (odds ratio, 3.00 [95% CI, 2.09–4.34]). Compared with children from normal-weight fathers, children from obese fathers also had an increased risk of childhood overweight (odds ratio, 2.52 [95% CI, 2.04–3.12]) but not of clustering of childhood cardiometabolic risk factors.

Discussion

We observed that higher maternal and paternal prepregnancy BMI were associated with increased adiposity levels and an adverse cardiometabolic profile in their children. Associations of maternal prepregnancy BMI with childhood outcomes tended to be stronger compared with associations of paternal BMI.

Methodological Considerations

Strengths of this study were the prospective data collection from early pregnancy onward, large sample size, and detailed childhood body fat and cardiometabolic measurements. Follow-up data were available in 70% of our study population. The nonresponse could lead to biased effect estimates if associations of parental BMI with childhood adiposity and

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Table 2. Parental Body Mass Index and Childhood Fat Mass Measures (N=4871)

Model	Body Mass Index (SDS)	Total Fat Mass (SDS)	Android/Gynoid Fat Mass Ratio (SDS)	Subcutaneous Abdominal Fat Mass Area (SDS)	Preperitoneal Abdominal Fat Mass Area (SDS)
Maternal model					
Basic model*	0.27 (0.24 to 0.29)†	0.25 (0.22 to 0.27)†	0.18 (0.15 to 0.21)	0.22 (0.19 to 0.25)†	0.17 (0.14 to 0.19)
Confounder model‡	0.25 (0.23 to 0.28)†	0.19 (0.17 to 0.21)†	0.15 (0.12 to 0.18)	0.16 (0.14 to 0.19)	0.12 (0.09 to 0.15)
Mediator models§					
Pregnancy complications	0.25 (0.23 to 0.28)	0.19 (0.16 to 0.21)	0.15 (0.12 to 0.18)	0.17 (0.14 to 0.19)	0.12 (0.09 to 0.15)
Maternal weight gain during pregnancy	0.28 (0.25 to 0.31)	0.20 (0.18 to 0.23)	0.16 (0.13 to 0.19)	0.17 (0.14 to 0.20)	0.13 (0.10 to 0.16)
Birth characteristics	0.23 (0.20 to 0.25)	0.19 (0.17 to 0.22)†	0.15 (0.13 to 0.18)	0.16 (0.14 to 0.19)	0.12 (0.09 to 0.15)
Infant growth	0.25 (0.22 to 0.27)†	0.19 (0.16 to 0.21)†	0.15 (0.12 to 0.18)	0.16 (0.13 to 0.19)†	0.12 (0.09 to 0.15)
Childhood BMI	…	0.02 (0 to 0.04)	–0.02 (–0.04 to 0.01)	0 (–0.02 to 0.03)	0 (–0.03 to 0.03)
Fully adjusted model‖	0.19 (0.16 to 0.22)†	0.03 (0.01 to 0.05)	–0.02 (–0.04 to 0.01)	0.01 (–0.02 to 0.03)	0 (–0.03 to 0.03)
Paternal model					
Basic model*	0.22 (0.19 to 0.24)†	0.18 (0.15 to 0.20)†	0.14 (0.11 to 0.17)	0.16 (0.12 to 0.19)†	0.12 (0.09 to 0.16)
Confounder model‡¶	0.22 (0.19 to 0.24)†	0.15 (0.12 to 0.17)†	0.13 (0.10 to 0.16)	0.13 (0.10 to 0.16)	0.10 (0.07 to 0.13)
Mediator models§					
Birth characteristics	0.20 (0.18 to 0.23)	0.15 (0.12 to 0.17)†	0.13 (0.10 to 0.16)	0.12 (0.09 to 0.15)	0.10 (0.06 to 0.13)
Infant growth	0.19 (0.16 to 0.22)†	0.13 (0.11 to 0.16)†	0.12 (0.09 to 0.15)	0.12 (0.09 to 0.15)†	0.09 (0.06 to 0.12)
Childhood BMI	…	0.01 (–0.01 to 0.03)	0 (–0.03 to 0.02)	0 (–0.02 to 0.03)	0 (–0.03 to 0.03)
Fully adjusted model#	0.14 (0.11 to 0.16)†	0.01 (–0.01 to 0.03)	0 (–0.02 to 0.03)	0 (–0.02 to 0.03)	0.01 (–0.03 to 0.04)
Combined maternal and paternal model					
Basic model*					
Maternal BMI	0.21 (0.18 to 0.24)†	0.20 (0.17 to 0.23)†	0.14 (0.11 to 0.17)	0.18 (0.15 to 0.21†	0.13 (0.09 to 0.16)
Paternal BMI	0.17 (0.15 to 0.20)†	0.13 (0.11 to 0.16)†	0.11 (0.08 to 0.14)	0.12 (0.09 to 0.15)†	0.10 (0.07 to 0.13)
Confounder model‡**					
Maternal BMI	0.21 (0.18 to 0.24)	0.16 (0.13 to 0.19)†	0.12 (0.09 to 0.15)	0.14 (0.11 to 0.18)†	0.10 (0.06 to 0.13)
Paternal BMI	0.18 (0.15 to 0.21)	0.12 (0.09 to 0.14)†	0.11 (0.08 to 0.14)	0.10 (0.07 to 0.13)†	0.08 (0.05 to 0.11)
Fully adjusted model††					
Maternal BMI	0.16 (0.13 to 0.19)†	0.03 (0.01 to 0.05)	–0.02 (–0.05 to 0.01)	0.02 (–0.01 to 0.05)	0.01 (–0.03 to 0.05)
Paternal BMI	0.11 (0.09 to 0.14)†	0.01 (–0.01 to 0.03)	0 (–0.02 to 0.03)	0 (–0.03 to 0.02)	0 (–0.03 to 0.04)

Values are regression coefficients (95% confidence interval [CI]) from linear regression models that reflect differences in childhood outcomes in SDS per SDS change in maternal and paternal prepregnancy body mass index (BMI). Estimates are based on multiple imputed data.

*Basic model includes child sex and age at outcome measurements.

†$P<0.05$ for heterogeneity between maternal and paternal associations.

‡Confounder model includes maternal age, educational level, ethnicity, parity, smoking and alcohol consumption during pregnancy, folic acid supplement use, total calorie intake during pregnancy, cesarean delivery, breast-feeding duration, timing of introduction of solid foods, child average duration of watching television, and childhood height (for fat mass outcomes only).

§Intermediate models are confounder models additionally adjusted for each potential intermediate.

‖Fully adjusted maternal model includes all potential confounders and intermediates.

¶Paternal confounder model includes paternal age, paternal educational level, and paternal ethnicity instead of maternal age, maternal educational level, and maternal ethnicity.

#Fully adjusted paternal model includes all potential confounders and intermediates.

**Maternal and paternal combined confounder model includes both maternal and paternal confounders.

††Combined fully adjusted model includes all potential maternal and paternal confounders and intermediates.

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cardiometabolic measures would be different between children included and not included in the analyses. Assuming that parents and children with a higher BMI are less likely to participate in detailed adiposity and cardiometabolic follow-up, our estimates may be underestimated. Information on maternal prepregnancy weight was self-reported, which might have led to misclassification and underestimation of the observed effects. However, we observed similar results when we used maternal weight measured at enrollment in the study (results not shown). No information about maternal and paternal insulin–glucose status was available in our study cohort. To obtain further insight into the potential underlying mechanisms, it is of interest to perform similar analyses taking into account parental insulin and glucose levels. We had detailed

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Table 3. Parental Body Mass Index and Childhood Cardiometabolic Risk Factors (N=4871)

Model	Systolic Blood Pressure (SDS)	Diastolic Blood Pressure (SDS)	Total Cholesterol (SDS)	HDL Cholesterol (SDS)	LDL Cholesterol (SDS)	Triglycerides (SDS)	Insulin (SDS)
Maternal model							
Basic model*	0.10 (0.07 to 0.12)	0.04 (0.01 to 0.07)	0.01 (−0.03 to 0.04)	−0.02 (−0.05 to 0.02)	0.02 (−0.02 to 0.05)	0.02 (−0.01 to 0.06)	0.04 (0 to 0.07)
Confounder model†	0.08 (0.05 to 0.11)	0.02 (−0.01 to 0.05)	−0.01 (−0.05 to 0.03)	−0.04 (−0.08 to 0)	0 (−0.03 to 0.04)	0.03 (−0.01 to 0.06)	0.05 (0.01 to 0.08)
Mediator models‡							
Pregnancy complications	0.07 (0.04 to 0.10)	0.01 (−0.02 to 0.04)	−0.01 (−0.05 to 0.03)	−0.04 (−0.07 to 0)	0 (−0.04 to 0.04)	0.03 (−0.01 to 0.06)	0.04 (0.01 to 0.08)
Maternal weight gain during pregnancy	0.09 (0.06 to 0.12)	0.02 (−0.01 to 0.05)	−0.01 (−0.05 to 0.02)	−0.05 (−0.08 to −0.01)	0.01 (−0.03 to 0.04)	0.03 (−0.01 to 0.07)	0.05 (0.01 to 0.09)
Birth characteristics	0.08 (0.05 to 0.11)	0.03 (0 to 0.06)	−0.01 (−0.04 to 0.03)	−0.04 (−0.08 to 0)	0.01 (−0.03 to 0.04)	0.03 (−0.01 to 0.07)	0.05 (0.02 to 0.09)
Infant growth	0.08 (0.05 to 0.11)	0.02 (−0.01 to 0.05)	-0.01 (−0.05 to 0.03)	−0.04 (−0.08 to 0)	0 (−0.03 to 0.04)	0.03 (−0.01 to 0.06)	0.05 (0.01 to 0.09)
Childhood BMI	0.02 (−0.01 to 0.05)	0 (−0.03 to 0.03)	−0.04 (−0.08 to 0)	−0.02 (−0.05 to 0.02)	−0.02 (−0.06 to 0.02)	−0.01 (−0.05 to 0.03)	−0.01 (−0.04 to 0.03)
Fully adjusted model§	0.04 (0.01 to 0.07)	0.01 (−0.03 to 0.04)	−0.04 (−0.08 to 0)	−0.02 (−0.06 to 0.03)	−0.02 (−0.06 to 0.02)	−0.01 (−0.05 to 0.03)	0 (−0.04 to 0.04)
Paternal model							
Basic model*	0.07 (0.04 to 0.10)	0.03 (0 to 0.06)	0 (−0.04 to 0.04)	−0.03 (−0.07 to 0.01)	0.01 (−0.03 to 0.05)	0.02 (−0.02 to 0.06)	0.01 (−0.03 to 0.05)
Confounder model†, ‖	0.06 (0.03 to 0.09)	0.02 (−0.01 to 0.05)	−0.01 (−0.05 to 0.03)	−0.05 (−0.08, −0.01)	0.01 (−0.03 to 0.05)	0.02 (−0.03 to 0.06)	0.01 (−0.03 to 0.05)
Mediator models‡							
Birth characteristics	0.06 (0.03 to 0.09)	0.02 (−0.01 to 0.06)	-0.01 (−0.05 to 0.04)	−0.04 (−0.08 to 0)	0.01 (−0.03 to 0.05)	0.02 (−0.02 to 0.06)	0.01 (−0.03 to 0.05)
Infant growth	0.05 (0.02 to 0.08)	0.02 (−0.02 to 0.05)	−0.01 (−0.05 to 0.03)	−0.04 (−0.08 to 0)	0.01 (−0.03 to 0.05)	0.02 (−0.02 to 0.06)	0 (−0.04 to 0.04)
Childhood BMI	0.02 (−0.02 to 0.05)	0.01 (−0.02 to 0.04)	−0.02 (−0.07 to 0.02)	−0.02 (−0.06 to 0.02)	−0.01 (−0.05 to 0.03)	−0.02 (−0.06 to 0.03)	−0.04 (−0.08 to 0)
Fully adjusted model¶	0.01 (−0.02 to 0.05)	0.01 (−0.03 to 0.04)	−0.02 (−0.06 to 0.02)	−0.02 (−0.06 to 0.02)	−0.01 (−0.05 to 0.03)	−0.01 (−0.05 to 0.03)	−0.04 (−0.08 to 0)
Combined maternal and paternal model							
Basic model*							
Maternal BMI	0.08 (0.05 to 0.12)	0.03 (0 to 0.07)	0.01 (−0.03 to 0.05)	−0.02 (−0.07 to 0.02)	0.03 (−0.01 to 0.07)	0.02 (−0.02 to 0.07)	0.02 (−0.02 to 0.07)
Paternal BMI	0.05 (0.02,0.09)	0.03 (−0.01 to 0.06)	0 (−0.04 to 0.04)	−0.03 (−0.07 to 0.01)	0.01 (−0.04 to 0.05)	0.01 (−0.03 to 0.05)	0 (−0.04, 0.05)
Confounder model†, #							
Maternal BMI	0.07 (0.04 to 0.10)	0.02 (−0.02 to 0.05)	−0.01 (−0.05 to 0.04)	−0.04 (−0.08 to 0.01)	0.02 (−0.03 to 0.06)	0.03 (−0.02 to 0.07)	0.03 (−0.01 to 0.08)
Paternal BMI	0.05 (0.01 to 0.08)	0.02 (−0.02 to 0.05)	−0.01 (−0.05 to 0.04)	−0.04 (−0.08 to 0)	0 (−0.04,0.04)	0.01 (−0.03 to 0.06)	0 (−0.04 to 0.04)
Fully adjusted model**							
Maternal BMI	0.05 (0.01 to 0.08)	0.01 (−0.03,0.05)	−0.04 (−0.08 to 0.01)	−0.01 (−0.06 to 0.04)	−0.01 (−0.06 to 0.04)	−0.01 (−0.05 to 0.04)	−0.02 (−0.07 to 0.03)
Paternal BMI	0.01 (−0.03 to 0.03)	0 (−0.03 to 0.04)	−0.02 (−0.06 to 0.02)	−0.02 (−0.06 to 0.02)	−0.01 (−0.05 to 0.03)	−0.01 (−0.05 to 0.03)	−0.04 (−0.08 to 0.01)

Values are regression coefficients (95% confidence interval [CI]) from linear regression models that reflect differences in childhood outcomes in SDS per SDS change in maternal and paternal prepregnancy body mass index (BMI). Estimates are based on multiple imputed data. All *P* values for heterogeneity between maternal and paternal associations are not significant. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

*Basic model includes child sex and age at outcome measurements.

†Confounder model includes maternal age, educational level, ethnicity, parity, smoking and alcohol consumption during pregnancy, folic acid supplement use, total calorie intake during pregnancy, cesarean delivery, breast-feeding duration, timing of introduction of solid foods, and child average duration of watching television.

‡Intermediate models are confounder models additionally adjusted for each potential intermediate.

§Fully adjusted maternal model includes all potential confounders and intermediates.

‖Paternal confounder model includes paternal age, paternal educational level and paternal ethnicity instead of maternal age, maternal educational level, and maternal ethnicity.

¶Fully adjusted paternal model includes all potential confounders and intermediates.

#Maternal and paternal combined confounder model includes both maternal and paternal confounders.

**Combined fully adjusted model includes all potential maternal and paternal confounders and intermediates.

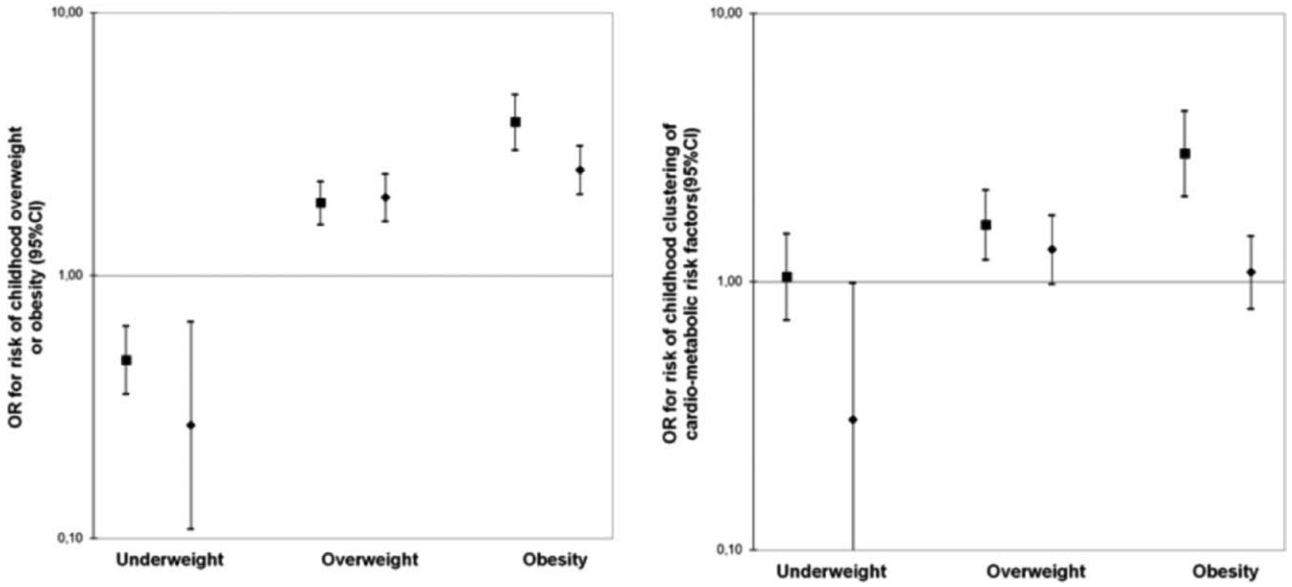

Figure. Associations of maternal and paternal underweight, overweight, and obesity with the risks of childhood overweight and childhood clustering of cardiometabolic risk factors (n=4871). **A**, Childhood overweight and obesity. **B**, Childhood clustering of cardiometabolic risk factors. ■, maternal association; ◆, paternal association. Values are odds ratios (ORs; 95% confidence interval [CI]) from logistic regression models that reflect the risks of childhood overweight and obesity and childhood clustering of cardiometabolic risk factors for maternal and paternal underweight, overweight, and obesity compared with the reference group (maternal and paternal normal weight). Estimates are based on multiple imputed data. Maternal models include child sex and age at outcome measurements, maternal age, educational level, ethnicity, parity, smoking and alcohol consumption during pregnancy, folic acid supplement use, total calorie intake during pregnancy, cesarean delivery, breast-feeding duration, timing of introduction of solid foods, and child average duration of watching television. Paternal models include paternal age, paternal educational level and paternal ethnicity instead of maternal age, maternal educational level, and maternal ethnicity.

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information about potential confounding factors available in this study. However, because of the observational design, residual confounding because of other lifestyle-related variables, such as parental and childhood nutritional intake, might still be an issue.

Interpretation of Main Findings

Previous studies showed that maternal obesity is associated with offspring obesity and an adverse cardiometabolic profile.[22] These associations may be explained by direct intrauterine mechanisms or shared environmental, lifestyle-related, or genetic characteristics. By comparing maternal–offspring and paternal–offspring associations, underlying mechanisms may be further elucidated.[6,7]

Previous studies examining the strengths of associations of both maternal and paternal prepregnancy BMI with childhood outcomes have mainly focused on childhood BMI and have reported inconsistent results.[5,8–11,23–25] Most studies reported no differences in the magnitude of parental associations with offspring BMI.[8–11,24] However, in childhood, BMI might not be an appropriate measure of fat mass. A study among 4091 UK parent–offspring trios reported that maternal prepregnancy BMI was more strongly associated with childhood fat mass, whereas in the same sample, similar effect estimates for the associations of maternal and paternal BMI with childhood BMI were reported.[8,9] A study among 89 parent–offspring pairs showed that maternal, but not paternal, BMI was an important determinant of childhood total fat mass.[26] Compared with paternal BMI, we observed that maternal BMI tended to be more strongly associated with childhood BMI, total body fat mass, android/gynoid fat mass ratio, abdominal subcutaneous and preperitoneal fat mass, which is a measure of visceral fat mass. In addition, the association of maternal, but not paternal, prepregnancy BMI with childhood total body fat mass was independent of childhood current BMI. Thus, our results suggest that children from mothers with a higher prepregnancy BMI have a higher total body fat mass, independent of their BMI, and relatively more abdominal fat mass. These specific total body and abdominal fat distribution measures are related to adult cardiometabolic disease and risk of mortality.[27,28]

Parental BMI has also been associated with separate cardiometabolic risk factors and clustering of these risk factors in offspring. A study among 3864 UK children showed that maternal and paternal prepregnancy BMI were significantly associated with offspring systolic blood pressure at 5 years in the fully adjusted models.[29] Another study among 9328 parents and their children reported that only maternal BMI was significantly associated with offspring systolic blood pressure, whereas both maternal and paternal BMI were associated with offspring lipid levels and inflammatory markers, with similar effect estimates. These associations were modified by offspring BMI, and after adjustment for offspring adiposity levels, most associations attenuated or reversed.[30] Among 940 Swedish children and 873 adolescents, it was shown that only maternal weight status influenced offspring cardiorespiratory fitness, after taking offspring fatness into account.[25] A study among 599 US children and their parents showed that both maternal and paternal BMI were associated with offspring risk of clustering of cardiovascular risk factors.[31] In this study, stronger associations for maternal BMI tended to be present. We observed that

only higher maternal prepregnancy BMI was associated with higher childhood systolic blood pressure. No associations of parental BMI with childhood metabolic measures were present after adjustment for childhood BMI. Maternal and paternal BMI were associated with the risk of childhood overweight, whereas only maternal BMI was associated with the risk of clustering of cardiometabolic risk factors.

The associations of maternal prepregnancy BMI with these childhood body fat distribution and cardiometabolic outcomes were strongest for maternal obesity but were also present across the full range. Although the observed effect estimates were small to moderate, these childhood cardiometabolic risk factors tend to track from childhood into adulthood and are associated with cardiovascular disease in later life.[32–36] Thus, these results suggest that especially maternal prepregnancy BMI may be a critical factor for offspring cardiometabolic health in later life.

The associations of maternal prepregnancy BMI with childhood outcomes may be explained by several mechanisms. Shared family-based, lifestyle-related characteristics and genetic factors are likely to explain part of the associations. Previously, we have shown that overweight and obese mothers differ from normal-weight mothers in sociodemographic and lifestyle-related characteristics.[37] However, for all childhood adiposity outcomes, systolic blood pressure, insulin, and clustering of cardiometabolic risk factors associations of maternal prepregnancy BMI tended to be stronger than associations of paternal BMI. In addition, extensive adjustment for sociodemographic and lifestyle-related characteristics did not explain our findings. The observed effects were also not mediated by pregnancy complications, birth characteristics, or infant growth, which are all identified risk factors related to both maternal prepregnancy BMI and health of offspring.[38–41] Thus, our findings suggest that associations of maternal prepregnancy BMI with offspring cardiometabolic health outcomes may, at least partly, be explained by direct intrauterine mechanisms. This may include higher maternal plasma concentrations and placental transfer of glucose, amino acids, and free fatty acids during pregnancy, which may influence programming of offspring adiposity and an adverse cardiometabolic profile in later life.[22,42] Further research is needed to obtain further insight into the causality and underlying mechanisms of these associations.

Perspectives

Both maternal and paternal prepregnancy BMI are associated with increased adiposity levels and an adverse cardiometabolic profile in offspring, with stronger associations present for maternal prepregnancy BMI. Preventive strategies that focus on reduction of obesity in pregnant women may lead to better cardiometabolic health in their offspring.

Acknowledgments

We gratefully acknowledge the contribution of general practitioners, hospitals, midwives, and pharmacies in Rotterdam.

Sources of Funding

The general design of the Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, Erasmus University Rotterdam, Netherlands Organization for Health Research and Development (ZonMw), Netherlands Organisation for Scientific Research, Ministry of Health, Welfare and Sport, and Ministry of Youth and Families. Research leading to these results has received funding from an unrestricted grant from Nutricia and the European Union's Seventh Framework Programme (FP7/2007–2013), project EarlyNutrition under grant agreement no. 289346. Vincent Jaddoe received an additional grant from the Netherlands Organization for Health Research and Development (VIDI 016.136.361). Drs Felix and Franco work in ErasmusAGE, a center for aging research across the life course funded by Nestlé Nutrition (Nestec Ltd), Metagenics Inc, and AXA.

Disclosures

None.

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Novelty and Significance

What Is New?

- Higher maternal and paternal prepregnancy body mass index (BMI) were associated with a higher childhood BMI, total body and abdominal fat mass measures, systolic blood pressure, and insulin levels and lower high-density lipoprotein cholesterol levels, with stronger associations present for maternal prepregnancy BMI.
- The associations of maternal prepregnancy BMI with childhood outcomes were not explained by maternal pregnancy complications, maternal gestational weight gain, birth characteristics, or infant growth.
- The associations of maternal prepregnancy BMI with childhood fat mass measures and cardiometabolic outcomes attenuated after adjustment for childhood current BMI.

What Is Relevant?

- These findings suggest that maternal prepregnancy BMI might be an important risk factor for cardiometabolic health of offspring and that at least part of the underlying mechanisms for this association may involve direct intrauterine mechanisms.

Summary

Both maternal and paternal prepregnancy BMI were associated with increased adiposity levels and an adverse cardiometabolic profile in offspring, with stronger associations present for maternal prepregnancy BMI. These associations are largely mediated by childhood BMI.

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